REVIEW

Rhinosinusitis Diagnosis and Management for the Clinician: A Synopsis of Recent Consensus Guidelines

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Rhinosinusitis (RS) affects approximately 1 in 7 adults in the United States, and its effect on quality of life, productivity, and finances is substantial. During the past 10 years, several expert panels from authoritative bodies have published evidence-based guidelines for the diagnosis and management of RS and its subtypes, including acute viral RS, acute bacterial RS, chronic RS (CRS) without nasal polyposis, CRS with nasal polyposis, and allergic fungal RS. This review examines and compares the recommendations of the Rhinosinusitis Initiative, the Joint Task Force on Practice Parameters, the Clinical Practice Guideline: Adult Sinusitis, the European Position Paper on Rhinosinusitis and Nasal Polyps 2007, and the British Society for Allergy and Clinical Immunology. Points of consensus and divergent opinions expressed in these guidelines regarding classification, diagnosis, and management of adults with acute RS (ARS) and CRS and their various subtypes are highlighted for the practicing clinician. Key points of agreement regarding therapy in the guidelines for ARS include the efficacy of symptomatic treatment, such as intranasal corticosteroids, and the importance of reducing the unnecessary use of antibiotics in ARS; however, guidelines do not agree precisely regarding when antibiotics should be considered as a reasonable treatment strategy. Although the guidelines diverge markedly on the management of CRS, the diagnostic utility of nasal airway examination is acknowledged by all. Important and relevant data from MEDLINE-indexed articles published since the most recent guidelines were issued are also considered, and needs for future research are discussed.

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ABRS = acute bacterial RS; AFRS = allergic fungal RS; AR = allergic rhinitis; ARS = acute RS; AVRS = acute viral RS; BSACI = British Society for Allergy and Clinical Immunology; CPG:AS = Clinical Practice Guideline: Adult Sinusitis; CRS = chronic RS; CT = computed tomography; EP³OS = European Position Paper on Rhinosinusitis and Nasal Polyps 2007; FDA = US Food and Drug Administration; JTFPP = Joint Task Force on Practice Parameters; NP = nasal polyposis; RI = Rhinosinusitis Initiative; RS = rhinosinusitis; VAS = visual analog scale

Rhinosinusitis (RS) poses a major health problem, substantially affecting quality of life, productivity, and finances. According to a recent analysis of US National Health Interview Survey data, RS affects approximately 1 in 7 adults.[1] The number of workdays missed annually because of RS was similar to that reported for acute asthma (5.67 days vs 5.79 days, respectively), and patients with RS were more likely to spend greater than $500 per year on health care than were people with chronic bronchitis, ulcer disease, asthma, and hay fever (all, $P<.001$).[2] Other data suggest that chronic RS (CRS) affects certain general health domains (social functioning, bodily pain) more than angina, chronic heart failure, chronic obstructive pulmonary disease, or chronic back pain.[3]

Although a common illness, RS presents a number of diagnostic and management challenges to the practicing clinician. *Rhinosinusitis* is the broad umbrella term covering multiple disease entities, including acute RS (ARS), CRS, and nasal polyposis (NP).[4] However, RS has numerous subtypes and distinct etiologies, wide variations in severity and clinical presentation, and overlapping symptomatology and/or pathology with other medical conditions. Simple and accurate office-based testing methods for its detection are lacking.

During the past decade, a number of expert panels have put forth evidence-based guidelines for the diagnosis and management of RS, including its subtypes.[4-7] Table 1 lists the organizations contributing to each of the projects: the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 (EP³OS),[4] the Rhinosinusitis Initiative (RI),[5,9] the Joint Task Force on Practice Parameters (JTFPP),[6] and the Clinical Practice Guideline: Adult Sinusitis (CPG:AS).[7] Another, comparatively brief, guideline has been released by the British Society for Allergy and Clinical Immunology (BSACI)[8]; its recommendations frequently correspond with those of the EP³OS. These guidelines draw from the evidence base of the published literature and reflect as well the viewpoints of many leading experts in the fields of allergy, immunology, and otolaryngology. Intended to benefit the practicing clinician, this review compares the recommendations made for the diagnosis and management of RS in these 5 guidelines and evaluates the sometimes limited and contradictory evidence that underpins them and the variable quality of the studies that produced that evidence. Significant, relevant data published in MEDLINE-indexed articles since the most recent guidelines were issued are

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Article Highlights

- Guidelines promulgated by 5 major groups regarding acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) are not in complete agreement regarding best practices
- Clinicians continue to overprescribe antibiotics for ARS. Antibiotics are appropriate in cases of severe ARS, although standards of severity vary. The value of antibiotics for treatment of CRS is still unproven
- The efficacy of intranasal corticosteroids has been well established by clinical trial data, and guidelines advise their use in ARS and CRS
- Although some groups have proposed management plans for CRS, a lack of adequate clinical trial data makes it difficult to ensure that treatment recommendations are based on rigorous evidence
- There has been a push for clinical trials examining CRS with nasal polyposis, CRS without nasal polyposis, and allergic fungal rhinosinusitis as distinct entities; however, few such trials have been conducted to date, and more data are needed to help clinicians treat these conditions appropriately

also reviewed. Key recommendations for diagnosis and treatment are indicated throughout the article in italics. As it is beyond the scope of this review to address the entire contents of these guidelines, the reader is encouraged to refer to the original documents.

RHINOSINUSITIS NOMENCLATURE

Rhinosinusitis vs Sinusitis

Of the 5 guidelines and expert panel documents, 4 (EP^{3}OS, RI, CPG:AS, and BSACI)[4,5,7,8] have adopted the term *rhinosinusitis* in place of *sinusitis*, the exception being the JTFPP.[6] The term *rhinosinusitis* may be more appropriate given that the nasal middle turbinate extends directly into the ethmoid sinuses, and effects on the middle turbinate may be seen in the anterior ethmoid sinuses as well. Clinically, sinus inflammation (ie, sinusitis) rarely occurs without concomitant inflammation of the contiguous nasal mucosa.[7] Regardless, the expert panels that adopted *rhinosinusitis* acknowledged that the terms *rhinosinusitis* and *sinusitis* should be used interchangeably, especially because the term *rhinosinusitis* has only come into common use during the past decade.

Classification by Duration of Symptoms

Of the various subclassifications of RS, the simplest differentiation is based on duration of symptoms. Acute RS is defined by 3 of the guidelines (RI, JTFPP, and CPG:AS) as symptom duration of 4 weeks or less.[5-7] The EP^{3}OS[4] and BSACI[8] guidelines qualify ARS as lasting less than 12 weeks, with complete resolution of symptoms. The CPG:AS includes a category of subacute RS, defined as symptom duration between 4 and 12 weeks,[7] whereas the JTFPP[6] definition specifies 4 to 8 weeks. Recurrent ARS is classified by the CPG:AS guidelines as 4 or more episodes of ARS within 1 year, without persistent symptoms between episodes.[7] The JTFPP defines recurrent RS as 3 or more episodes per year.[6]

Four of the 5 guidelines (EP^{3}OS,[4] RI,[5] CPG:AS,[7] and BSACI[8]) designate CRS as symptoms persisting 12 weeks or longer, whereas the JTFPP[6] indicates 8 weeks.

Classification by Severity of Symptoms

All 5 guidelines recognize that *an assessment of symptom severity is important to define the magnitude of disease and assist with treatment selection.* For clinical purposes, the EP^{3}OS and BSACI guidelines categorize disease severity on the basis of a 10-cm visual analog scale (VAS) that has been statistically validated for use in patients with RS. Patients responding to the question "How troublesome are your symptoms of rhinosinusitis?" provide a rating, with the scale ranging from 0 ("not troublesome") to 10 ("worst thinkable troublesome"). Scores are categorized as follows, between 0 and 3, mild disease; greater than 3 to 7, moderate disease;

TABLE 1. **Recent Evidence-Based Guidelines for the Diagnosis and Treatment of Rhinosinusitis**

Reference	Guideline designation	Representation of contributors
Fokkens et al,[4] 2007	EP^{3}OS	Task force commissioned by the EAACI
Meltzer et al,[5] 2004	RI	Joint consensus of the major US allergy/ENT associations: AAAAI, AAOA, AAO-HNS, ACAAI, and ARS
Slavin et al,[6] 2005	JTFPP	AAAAI, ACAAI, and the Joint Council of Allergy, Asthma and Immunology
Rosenfeld et al,[7] 2007	CPG:AS	Panel selected by the AAO-HNS Foundation
Scadding et al,[8] 2008	BSACI	Standards of Care Committee of the BSACI

AAAAI = American Academy of Allergy, Asthma and Immunology; AAOA = American Academy of Otolaryngic Allergy; AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; ACAAI = American College of Allergy, Asthma and Immunology; ARS = American Rhinologic Society; BSACI = British Society for Allergy and Clinical Immunology; CPG:AS = Clinical Practice Guideline: Adult Sinusitis; EAACI = European Academy of Allergy (formerly Allergology) and Clinical Immunology; ENT = ear, nose, and throat; EP^{3}OS = European Position Paper on Rhinosinusitis and Nasal Polyps 2007; JTFPP = Joint Task Force on Practice Parameters; RI = Rhinosinusitis Initiative.

TABLE 2. **Summary of Recent Evidence-Based Guidelines for the Diagnosis of ARS (Suspected AVRS or ABRS)[a,b]**

Guideline	Hallmark signs and symptoms	Diagnostic criteria and definitions	Special assessments
EP³OS,[4] 2007	Inflammation of the nose and paranasal sinuses characterized by ≥2 symptoms, 1 of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) ± Facial pain/pressure ± Reduction or loss of smell	Presumed AVRS Duration of symptoms <10 d Presumed ABRS Increase of symptoms after 5 d of persistent symptoms Duration of symptoms >10 d	Not recommended Radiographic imaging CT (except in patients with severe disease, those who are immunocompromised, and those with suspected complications) Optional Anterior rhinoscopy Nasal endoscopy Nasal culture, in case of treatment failure or complications
RI,[5] 2004	Major symptoms Purulent-discolored anterior or posterior nasal drainage[c] Nasal obstruction/blockage[c] Facial congestion/fullness Facial pain/pressure/fullness[c] Hyposmia/anosmia Fever (acute only) Minor symptoms Headache Ear pain/pressure/fullness Halitosis Dental pain Cough Fever Fatigue	Required symptoms Anterior and/or posterior purulent drainage + nasal obstruction *OR* facial pain/pressure/fullness ABRS suspected if symptoms persist ≥10 d beyond the onset of upper respiratory symptoms, worsen within 10 d of initial improvement, or are particularly severe in the first 3-4 d of illness	Not required Radiography (in most cases) CT (except in recurrent cases and before surgery) Exception Diagnosis of ABRS requires objective documentation by either nasal airway examination for purulent drainage or radiographic evidence
JTFPP,[6] 2005	Symptoms Nasal congestion Purulent rhinorrhea Facial-dental pain Postnasal drainage Headache Cough Signs Tenderness overlying the sinuses Dark circles beneath the eyes	Presumed AVRS unless symptoms last >10-14 d or are unusually severe (eg, fever with purulent nasal discharge, facial pain or tenderness, periorbital swelling)	Not required Plain radiography Nasal cultures Optional Nasal endoscopy Nasal cytology Nasal endoscopy/other imaging studies, if initial treatment unsuccessful
CPG:AS,[7] 2007	3 cardinal symptoms Purulent nasal discharge (anterior, posterior, or both) accompanied by nasal obstruction, facial pain/pressure, or both	Presumed AVRS Symptoms present <10 d and are not worsening Presumed ABRS Symptoms persist ≥10 d beyond the onset of upper respiratory symptoms, worsen within 10 d of initial improvement, or are particularly severe in the first 3-4 d of illness	Not required Radiographic imaging (except in the event of a complication or if an alternative diagnosis is suspected) Nasal cultures Preferred CT (for evaluating complications of ARS)

[a] ABRS = acute bacterial RS; ARS = acute RS; AVRS = acute viral RS; CPG:AS = Clinical Practice Guideline: Adult Sinusitis; CT = computed tomography; EP³OS = European Position Paper on Rhinosinusitis and Nasal Polyps 2007; JTFPP = Joint Task Force on Practice Parameters; RI = Rhinosinusitis Initiative; RS = rhinosinusitis.

[b] These guidelines pertain to the diagnosis of ARS in clinical practice; clinical trial diagnostic requirements are more stringent.

[c] Cardinal symptoms of ABRS.

and greater than 7 to 10, severe disease.[4] Scores greater than 5 have been correlated with quality of life detriments.[10]

DIAGNOSIS OF ARS

Cardinal Signs or Symptoms

The expert guidelines demonstrate close agreement in their identification of the hallmark signs or symptoms of ARS; however, specific algorithms differ somewhat, as detailed in Table 2.[4-7] *Three major signs or symptoms are consistently cited across all the guidelines as being primary diagnostic indicators for ARS: nasal congestion, obstruction, or blockage; anterior and/or posterior purulent rhinorrhea (EP³OS[4] and BSACI[8] do not specify "purulent"); and facial pain or pressure.* The RI guidelines[5] state that a diagnosis of ARS is probable if 2 or more of these major symptoms

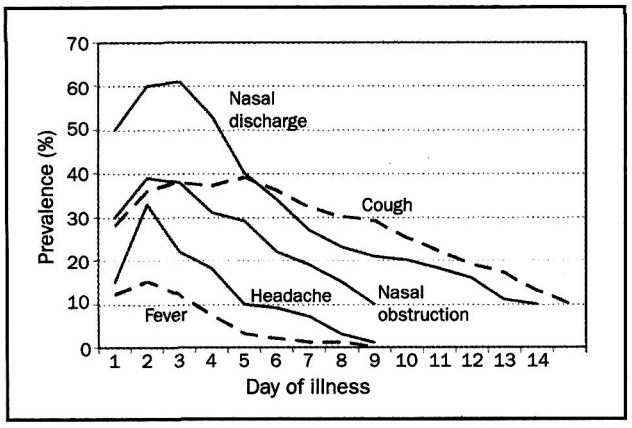

FIGURE 1. Normal pattern of symptom prevalence over time (days) for acute viral rhinosinusitis.
From Otolaryngol Head Neck Surg,[7] with permission from Elsevier. Data from *JAMA.*[10]

are present (the 3 already cited, as well as hyposmia-anosmia and fever), or 1 major symptom along with 2 or more minor symptoms (listed in Table 2). The JTFPP guidelines[6] include these 4 symptoms along with headache and cough as being indicative of ARS. The CPG:AS guidelines[7] require evidence of purulent nasal discharge for an ARS diagnosis, which must be accompanied by nasal obstruction, facial pain or pressure, or both. The EP^{3}OS guidelines[4] require the presence of 2 or more major symptoms, 1 of which must be either nasal discharge or nasal blockage, congestion, or obstruction; other symptoms can include facial pain or pressure or reduction or loss of smell. The BSACI guidelines[8] have these requirements plus characteristic signs on either endoscopy or computed tomography (CT). It should be noted that fever is cited as a possible diagnostic indicator only in the RI guidelines.[5]

Viral vs Bacterial Etiology

Acute RS is most commonly viral in origin (eg, the common cold). The incidence of acute viral RS (AVRS) is extremely high, estimated to occur from 2 to 5 times per year in an average adult.[4] Secondary bacterial infection is thought to complicate only a very small percentage of cases (0.5%-2.0%).[4] One of the primary challenges in managing ARS is the proper identification of cases with bacterial etiology.

Although the general presentation of AVRS and acute bacterial RS (ABRS) can be extremely similar, a particular emphasis on the *duration, pattern, and/or severity of symptoms* can help differentiate bacterial from viral illness. As illustrated in Figure 1,[7,10,11] AVRS symptoms typically peak within 2 to 3 days of onset, decline gradually thereafter, and disappear within 10 to 14 days. Thus, cases that deviate from this pattern are likely not viral. This remains one of the simplest and most reliable means of evaluating ARS etiology. Persistent symptoms between days 5 to 10 are the most difficult to assess, because they can represent either lingering evidence of viral disease or the beginning of bacterial infection.[7] *Four of the guidelines (all except the BSACI guidelines[8]) agree that symptoms persisting for 10 days or more and/or showing a pattern of initial improvement followed by worsening are likely bacterial in origin* (Table 2). Of the 5 guidelines,[5-9] 4 (RI, JTFPP, CPG:AS, and BSACI) suggest that unusually severe symptoms (eg, high fever, unilateral facial/tooth pain, orbital cellulitis, intracranial expansion), particularly during the first several days of disease, are also suggestive of ABRS. The JTFPP[6] and CPG:AS[7] guidelines indicate that neither nasal mucus color nor the presence of fever is useful in differentiating bacterial from viral disease.

The CPG:AS document highlights 3 cardinal symptoms with the highest relative specificity and sensitivity for ARS in general: *purulent nasal drainage* in the presence of *nasal obstruction* and/or *facial pain, pressure, or fullness* is the cornerstone of diagnosis.[7] Nasal purulence alone cannot distinguish between viral and bacterial infection, but a diagnosis of ABRS is unlikely in its absence, even when other cardinal symptoms are evident. In other words, specificity for ABRS increases when nasal obstruction or facial pain occurs in combination with nasal purulence. Isolated symptoms of nasal obstruction or facial pain could have a broad differential diagnosis, but when coupled with purulent nasal discharge, they become much more specific for ABRS, particularly when they persist longer than 10 days.[7]

Special Assessments

Acute RS can generally be diagnosed adequately on the basis of clinical findings alone, without the use of special imaging techniques or other assessments. However, the consensus guidelines recognize particular situations in which special assessments may have a role. According to all the guidelines, plain radiography is neither useful nor cost-effective. Computed tomography is not recommended as part of the routine work-up but is mentioned by some guidelines (EP^{3}OS and CPG:AS) as a preferred imaging option for cases characterized by severe disease, immunocompromised state, or suspected complications.[4,7] The RI guidelines recommend CT before surgery and for evaluation of cases with recurrent ARS. The JTFPP asserts that radiographic assessment is generally unnecessary, but imaging studies (CT, not plain radiography) can be useful in certain situations to support the diagnosis or establish the degree of mucosal involvement.[6] The BSACI guidelines recommend the use of CT but do not consider it a "primary investigation."[8]

Nasal Endoscopy. Compared with anterior nasal examination, nasal endoscopy provides a better means of examining the middle meatus region and sphenoethmoidal re-

cesses for the presence of purulence associated with ARS.[12] However, it is not available to most primary care physicians. Aside from the BSACI, the guidelines are in agreement that nasal endoscopy is not essential for the diagnosis of ARS.[8] The RI document states that nasal endoscopy might be indicated for evaluating cases refractory to empirical treatment, patients with unilateral disease without septal deviation, and patients with severe, disabling symptoms.[9] The JTFPP guidelines suggest considering nasal endoscopy during the initial work-up or in cases of treatment failure.[6]

Nasal Culture. Nasal culture is not generally recommended for the routine work-up of uncomplicated ARS (JTFPP, CPG:AS, BSACI)[6-8]; however, the EP^{3}OS guidelines[4] consider it an option in the event of treatment failure or complications. The RI guidelines[5] affirm that properly obtained endoscopic cultures can be useful to identify causative organisms in certain forms of RS.

Sinus Puncture. Although rarely indicated for routine patient care, sinus puncture is the methodology considered the criterion standard for confirming bacterial pathogens within the maxillary sinuses (EP^{3}OS, JTFPP, CPG:AS, RI).[4,6,7,9,13] As such, sinus puncture has most applicability in the clinical trial setting. However, the JTFPP mentions certain clinical situations that may warrant sinus puncture to obtain diagnostic cultures; for example, it may be useful in acute episodes that are refractory to treatment or for rapid and accurate identification of the causative organism in immunosuppressed patients.[5] Sinus puncture is typically performed by inserting a large-bore needle into the maxillary sinus through the inferior meatus or canine fossa.[9,14,15]

MANAGEMENT OF ARS

The fundamental issue in determining appropriate treatment is identifying which ARS cases warrant antibiotics. Survey data confirm a remarkable overuse of antibiotics for ARS that is most likely viral rather than bacterial. Only an estimated 0.5% to 2.0% of ARS episodes have a bacterial etiology. In addition, *the recent consensus documents discussed herein have reconsidered the appropriateness of antibiotic use for mild cases of presumed ABRS.* Clinical studies have confirmed that roughly 60% of presumed ABRS cases resolve spontaneously without antibiotics. Despite this compelling evidence indicating that antibiotics are overused, recent data from the United States and United Kingdom indicate that antibiotics are prescribed in 81% to 92% of ARS cases.[16,17] Unnecessary prescribing of antibiotics adds to treatment costs, puts patients at risk of adverse events, and adds to the growing problem of antimicrobial resistance.

Evidence-based treatment recommendations from EP^{3}OS, JTFPP, and CPG:AS are summarized in Table 3, along with their strength and level of evidence.[4,6,7] The graded evidence-based recommendations from BSACI simply note that the use of topical corticosteroids or an antihistamine together with antibiotics is associated with more rapid symptom resolution, and this is given a grade of A; elsewhere it is noted that antibiotics should be reserved for severe symptoms, such as maxillary pain, swelling, and fever.[8] Although the BSACI grading system is undefined, it appears similar to that used by the EP^{3}OS guidelines (Table 3). The key features for evaluating antibiotic appropriateness should be symptom severity and duration. *These 4 guidelines (all except BSACI) recommend antibiotics for any patient presenting with severe illness, and EP^{3}OS, JTFPP, and CPG:AS recommend antibiotics for those who do not show improvement beyond given time points or for those whose symptoms worsen* (see Table 3 for specific criteria). The EP^{3}OS guidelines recommend no treatment other than symptomatic relief for at least the first 5 days because this is the "window" of time when AVRS is still the most likely diagnosis. If symptoms persist or increase beyond 5 days, moderate cases should first be prescribed intranasal corticosteroids, with antibiotics added if no improvement occurs after 14 days; severe cases qualify for initial combination therapy with intranasal corticosteroids plus antibiotics.[4] The CPG:AS cautions that mucus color should not dictate antibiotic use because color relates to the presence of neutrophils, not bacteria.[7] Clearly, the intent of these key recommendations is to reduce the use of antibiotics for cases of AVRS and mild ABRS.

"Watchful waiting" and symptomatic relief are generally recommended initially for cases not meeting the criteria for antibiotic intervention. *The 4 guidelines with evidence-based ARS treatment recommendations (EP^{3}OS, JTFPP, CPG:AS, and BSACI) recognize the usefulness of intranasal corticosteroids, which is supported by strong evidence from multiple randomized controlled trials.*[4,6-8] However, it should be noted that intranasal corticosteroids are not approved by the US Food and Drug Administration (FDA) for treatment of ABRS.

The EP^{3}OS guidelines suggest that oral corticosteroids may be useful for pain relief in severe disease.[4] The use of topical or oral decongestants is acknowledged, but the EP^{3}OS, JTFPP, and CPG:AS guidelines conclude that sufficient data are lacking to fully evaluate the usefulness of these agents in ARS. Data on antihistamine use in ARS are also scarce; the JTFPP does not recommend their use,[6] whereas the CPG:AS, EP^{3}OS, and BSACI guidelines recognize their potential value in allergic patients.[4,7,8] The CPG:AS also recommends nasal saline irrigation.[7]

DIAGNOSIS OF CRS

Despite a good deal of overlap between ARS and CRS with regard to individual symptoms, CRS is much more hetero-

TABLE 3. **Summary of Recent Evidence-Based Recommendations for the Treatment of ARS**[a]

Guideline	Uncomplicated, presumed AVRS	ABRS	ARS in general
EP³OS,[4] 2007[b,c]	Mild disease Symptoms lasting <5 d or improving thereafter Relieve symptoms by using decongestants (Ib/D),[18-21] saline (Ib/D),[22,23] or analgesics Moderately severe Symptoms persisting or increasing after 5 d Add topical corticosteroids If no improvement after 14 d Reconsider diagnosis Perform nasal endoscopy Consider culture/imaging Prescribe oral antibiotics if indicated (Ib/A)[24-30] Severe Severe pain, temperature >38°C Add antibiotics (Ia/A)[31-34] and topical corticosteroids for 7-14 d (Ib/A)[24-30] (expect to see effect within 48 h)		Intranasal corticosteroids (Ib/A)[24-30] Oral corticosteroids to reduce pain in severe disease (Ib/A)[35,36] Oral antihistamines only in allergic patients (Ib/B)[37] Decongestants (Ib/D)[18-21]
JTFPP,[6] 2005[c]	7-10 d course of "watchful waiting" (ungraded) Antibiotics are inappropriate and discouraged strongly (D)	Antibiotics Primary therapy (A) (Ia,[38] Ia,[39] IV,[40] Ia,[41] IV,[42] III,[43] III,[44] Ia,[45] III,[46] Ib,[47] Ib,[48] Ib[49]) 10-14 d course (D) Choice of agent based on likely bacterial pathogens consistent with clinical history Consider in patients with severe signs/symptoms at any time (worsening after 3-5 d, temperature >39°C, maxillary tooth/facial pain, unilateral sinus tenderness, periorbital swelling)[38-49]	Intranasal corticosteroids Modestly beneficial as adjunctive therapy with antibiotics in patients with recurrent disease (C) (III,[50] Ib,[51] IIa,[52] IV,[53] IIa[54]) Antihistamines No data to recommend use (D) Topical and oral decongestants Do not use because prospective studies evaluating use are lacking (D)
CPG:AS,[7] 2007[d]	Management is primarily symptomatic Analgesics Antipyretics Oral/topical decongestants Topical nasal corticosteroids (optional, B/D)[55,56]	Assess pain and prescribe analgesic therapy as appropriate (strong recommendation, B evidence)[57,58] "Watchful waiting" (observation without antibiotics for ≤7 d after diagnosis) is an option for selected patients with uncomplicated disease or mild illness (mild pain, temperature <38.3°C) and who are likely to return for follow-up (B/C)[59-61] Initiate antibiotics if patient's condition does not improve by 7 d or worsens at any time (recommendation, B)[31,45,62] Use antibiotics initially in severe illness (moderate-severe pain, temperature ≥38.3°C); amoxicillin as first-line therapy (recommendation, B)[30,32,33,63-66] Antihistamines Do not use in patients with nonatopic disease (D)[6,37,60,76] Symptomatic relief if recommended	Topical corticosteroids Optional (B/C)[25-28,30] Nasal saline irrigation Optional (B)[18,67-70] Decongestants Optional (B/C)[71-75]

[a] ABRS = acute bacterial RS; ARS = acute RS; AVRS = acute viral RS; CPG:AS = Clinical Practice Guideline: Adult Sinusitis; EP³OS = European Position Paper on Rhinosinusitis and Nasal Polyps 2007; JTFPP = Joint Task Force on Practice Parameters; RCT = randomized clinical trial; RS = rhinosinusitis.

[b] These guidelines did not distinguish between presumed and uncomplicated AVRS and ABRS.

[c] **Strength of recommendation for EP³OS and JTFPP**: A, directly based on category I evidence; B, directly based on category II evidence or extrapolated recommendation from category I evidence; C, directly based on category III evidence or extrapolated recommendation from category I or II evidence; D, directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence. Grades of recommendation and level of evidence in the EP³OS guidelines were provided for the use of therapies for ARS and/or its subtypes, not the order or duration of these therapies. Order and duration of therapy choices presented here are taken from the treatment algorithm found in the EP³OS guidelines. **Categories of evidence for EP³OS and JTFPP**: Ia, from meta-analysis of RCTs; Ib, from ≥1 RCT; IIa, from ≥1 controlled study without randomization; IIb, from ≥1 other type of quasiexperimental study; III, from nonexperimental descriptive studies (eg, comparative studies, correlation studies, case-control studies); IV, from expert committee reports or opinions and clinical experience of respected authorities or both.

[d] **Strength of recommendation for CPG:AS**: A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B). In some clearly identified circumstances, strong recommendations may be made on the basis of lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C). In some clearly identified circumstances, recommendations may be made on the basis of lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms. *Optional* means either that the quality of evidence that exists is suspect (grade D) or that well-done studies (grade A, B, or C) show little clear advantage to one approach vs another. No recommendation means that pertinent evidence is lacking (grade D) and that the balance between benefits and harms is unclear. **Grades of Evidence for CPG:AS**: A, well-designed RCTs or diagnostic studies performed on a population similar to the guideline's target population; B, randomized controlled trials or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies; C, observational studies (case control and cohort design); D, expert opinion, case reports, reasoning from first principles (bench research or animal studies); X, exceptional situations in which validating studies cannot be performed and there is a clear preponderance of benefit over harm.

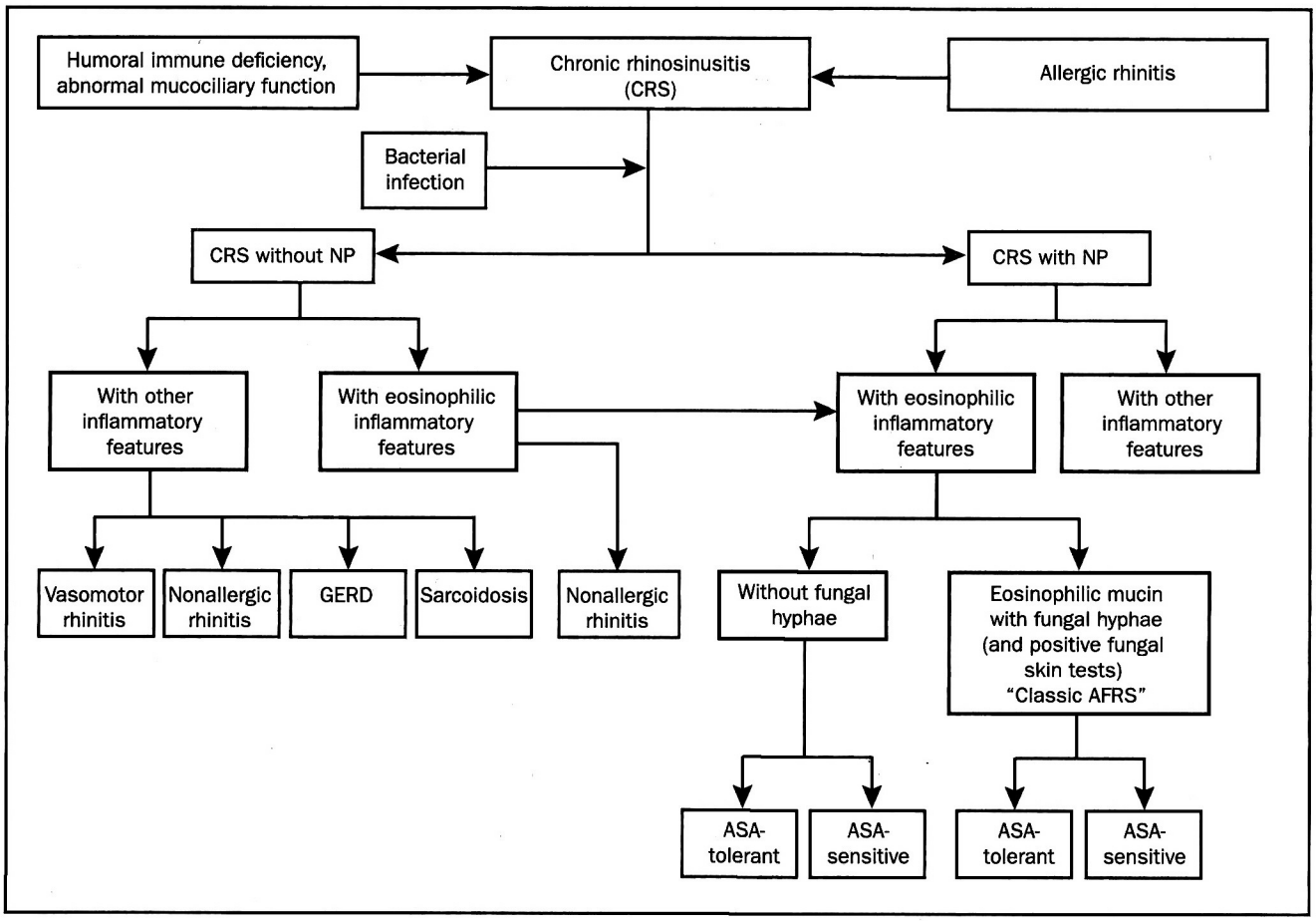

FIGURE 2. Proposed subclassification of chronic rhinosinusitis. AFRS = allergic fungal rhinosinusitis; ASA = aspirin; GERD = gastroesophageal reflux disease; NP = nasal polyposis.
From *J Allergy Clin Immunol*,[5] with permission from Elsevier.

geneous. The greater complexity of CRS is exemplified by a lack of agreement among leading authorities as to the categorization of the disease. Of the 5 consensus guidelines, the RI group has proposed the most detailed subclassification scheme to date (Figure 2).[5] In this scheme, the most important differentiating features are the presence or absence of the following: (1) NP, (2) eosinophilic or other inflammatory features, and (3) fungal hyphae in sinus mucus. Determination of inflammatory characteristics of the nasal mucosa requires evaluation of sinus tissue and/or sinus mucus. If such evaluations are not feasible in a clinical setting, the minimal recommended classification should at least differentiate between CRS with vs without NP. The proposed RI classification also takes into account other underlying or predisposing factors, such as mucus recirculation, humoral immune deficiency, abnormal mucociliary function, and allergic rhinitis (AR).[5] The role of fungal involvement in CRS continues to be a focus of research and debate. Fungal allergy and the presence of fungal hyphae in eosinophil-laden mucus (known as *allergic mucin*) are key features identifying a small subset of cases of allergic fungal RS (AFRS). However, many more patients with CRS show immune hyperresponsiveness to fungi such as *Alternaria* species, as evidenced by increased cytokine expression independent of IgE levels, indicating that nonallergic mechanisms also play a role.[77]

In contrast to ARS, CRS generally cannot be diagnosed on the basis of symptoms alone. In fact, the guidelines display a general similarity in outlining diagnostic parameters for CRS that combine symptom assessments with objective findings of some type. Objective evidence of chronic sinus disease helps to distinguish CRS from other possible causes of CRS-type symptoms, including neoplasm or other sources of headache or dental pain.

Cardinal Signs or Symptoms

Prolonged duration of RS symptoms (more than 8-12 weeks) is the primary reason to evaluate a patient for CRS.[7] In this regard, it is important to distinguish CRS

TABLE 4. **Summary of Recent Evidence-Based Guidelines for the Diagnosis of CRS[a,b]**

Guideline	Criteria for diagnosis	Special assessment recommendations
EP³OS,[4] 2007	≥2 symptoms lasting >12 wk, 1 of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) ± Facial pain/pressure ± Reduction or loss of smell Objective criteria Endoscopy or rhinoscopy to identify presence/absence of NP	Recommended Endoscopy Anterior rhinoscopy, if endoscopy unavailable Allergy testing, if history is suggestive Not recommended CT for primary care Optional CT for ENT specialists
RI,[5] 2004	CRS with or without NP ≥2 of the following symptoms for ≥12 wk Anterior and/or posterior mucopurulent drainage Nasal obstruction Facial pain/pressure/fullness (without NP only) Decreased sense of smell (with NP only) Objective criteria Nasal airway examination to confirm or exclude NP and/or to document inflammation Sinus CT not essential but should be strongly considered AFRS ≥1 of the symptoms already listed Objective criteria Endoscopy to document presence of allergic mucin[c] containing fungal hyphae or culturable fungi and inflammation (eg, edema of middle meatus or ethmoid area, NP) Evidence of fungus-specific IgE (by skin test or in vitro blood test) No histologic evidence of invasive fungal disease	Diagnosis of CRS with or without NP Strongly recommended Nasal airway examination, CT (not essential) Diagnosis of AFRS Recommended Skin test or in vitro blood test for fungus-specific IgE Endoscopy Fungal stain of allergic mucin Optional Fungal culture Total serum IgE Imaging by >1 technique (highly suggestive of diagnosis)
JTFPP,[6] 2005	Same symptoms as for ARS Varying severity Duration ≥8 wk May be vague or insidious Objective criteria Abnormal findings on CT or MRI expected	Recommended Allergy testing CT and MRI may be useful to confirm diagnosis in patients with vague symptoms or if symptoms persist despite optimal medical treatment CT is particularly helpful for diagnosis of AFRS Optional Nasal endoscopy Nasal-sinus biopsy
CPG:AS,[7] 2007	≥12-wk duration of ≥2 of the following Mucopurulent drainage Nasal obstruction Facial pain/pressure/fullness Decreased sense of smell *AND* Inflammation documented by ≥1 of the following objective criteria Purulent mucus or edema in the middle meatus or ethmoid region NP in nasal cavity or middle meatus Radiographic imaging showing inflammation of the paranasal sinuses	Recommended requirement for diagnosis Documentation of inflammation by examination through either nasal endoscopy or CT Optional Allergy/immunologic testing to rule out underlying causes of symptoms

[a] AFRS = allergic fungal rhinosinusitis; ARS = acute rhinosinusitis; CPG:AS = Clinical Practice Guideline: Adult Sinusitis; CRS = chronic rhinosinusitis; CT = computed tomography; ENT = ear, nose, and throat; EP³OS = European Position Paper on Rhinosinusitis and Nasal Polyps 2007; JTFPP = Joint Task Force on Practice Parameters; MRI = magnetic resonance imaging; NP = nasal polyposis; RI = Rhinosinusitis Initiative.

[b] These guidelines pertain to the diagnosis of CRS in clinical practice; clinical trial requirements are more stringent.

[c] Allergic mucin is thick, highly viscous mucus containing a dense accumulation of eosinophils that typically show signs of degranulation.

from recurrent ARS, the latter of which is typified by 2 to 4 isolated episodes of ARS per year, with complete resolution of symptoms between episodes. Such episodes should be treated like any other ARS event but also warrant further work-up to investigate potential underlying causes for the recurrence (eg, AR, cystic fibrosis, immunologic deficiency, ciliary dyskinesia, anatomic abnormalities).[7]

In general, individual symptoms of CRS are similar to those seen in ARS (anterior or posterior mucopurulent drainage; nasal obstruction; facial pain, pressure, or fullness) but may be milder or less dramatic and variable in presentation (Table 4).[4-7] Rare cases of CRS may display a single symptom.[5] A decreased sense of smell is identified by 4 guidelines (EP³OS, RI, CPF:AS, and BSACI)[4,5,7,8] as an important CRS symptom but by only 2 guidelines as a symptom diagnostic of ARS.[4,8] The EP³OS guidelines suggest additional minor symptoms of CRS, including ear pain or pressure, halitosis, dental pain, cough, fever,

and fatigue.[4] The EP³OS guidelines recommend evaluating the magnitude of symptom severity (mild, moderate, or severe), as discussed earlier for ARS, for purposes of treatment decisions.[4]

The RI, CPG:AS, and EP³OS guidelines are in relatively good agreement with regard to diagnostic symptom criteria. The RI guidelines[5] stipulate the persistence for 12 or more weeks of at least 2 of 4 possible symptoms: (1) nasal congestion; (2) anterior or posterior mucopurulent drainage; (3) facial pain, pressure, or fullness; and (4) a decreased sense of smell. Facial pain, pressure, or fullness is relatively more common in CRS without NP, whereas a decreased sense of smell is more common in CRS with NP. The CPG:AS stipulates that, when present for 12 or more weeks, any 2 of the same 4 symptoms are diagnostic for CRS in general.[7] The EP³OS and BSACI criteria are essentially the same as the CPG:AS, except that 1 of the hallmark symptoms must be either nasal discharge or nasal blockage and obstruction.[4,8]

Diagnostic Testing

In 4 guidelines, *the importance of diagnostic testing is a key difference between CRS and ARS* (Table 4).[4-7] Some form of nasal airway examination is recommended by 4 of the guidelines (EP³OS, RI, CPG:AS, and BSACI) to establish a CRS diagnosis. Supportive findings include purulent mucus or edema in the middle meatus or ethmoid region; the presence or absence of NP can be established with examination.[4,5,7,8] The JTFPP suggests that nasal endoscopy be considered in patients with CRS or ARS.[6] The EP³OS, RI, CPG:AS, and BSACI guidelines preferentially support nasal endoscopy over anterior rhinoscopy, although anterior rhinoscopy is cited as a basic, preliminary evaluation tool.[4,5,7] Nasal endoscopy allows better illumination and visualization of the posterior nasal cavity, nasopharynx, and sinus drainage pathways in the middle and superior meatus; it also allows delineation of nasal septal deviation, NP, and secretions in posterior regions. A 2010 study by Bhattacharyya and Lee[78] found that addition of nasal endoscopy to symptom assessment substantially increased diagnostic accuracy in confirming the presence of CRS using sinus CT as the criterion standard. Nasal endoscopy can also facilitate the procurement of endoscopic cultures that are useful in guiding antibiotic selection in appropriate cases.[5]

All 5 guidelines acknowledge that CT has particular value in evaluating suspected CRS; however, it fails to achieve the status of a routine, first-line recommendation (Table 4). The RI guidelines state that CT is not essential to a diagnosis of CRS but should be strongly considered.[5] The CPG:AS document requires objective documentation of inflammation, which can be achieved either by nasal endoscopy or CT.[7] The EP³OS guidelines actually recommend against CT for primary care work-up of RS and characterize it as an optional work-up for ear, nose, and throat specialists.[4]

The JTFPP guidelines assert that imaging techniques (CT or magnetic resonance imaging) may be useful in confirming a diagnosis in patients with vague symptoms or if symptoms persist despite optimal medical treatment.[6] A sinus CT may also be useful to identify structural abnormalities in the sinuses, bony erosion, or extrasinus involvement.[7] Certain "benign" conditions can also cause extrasinus involvement, such as bony erosion and/or mucocele formation, which are found in some cases of AFRS. Such findings may require further evaluation by magnetic resonance imaging (EP³OS and CPG:AS).[4,7] Magnetic resonance imaging, which provides an excellent display of the mucosa rather than of the bony anatomy, may be particularly useful in distinguishing bacterial or viral inflammation from fungal concretions (RI).[5]

Plain radiography has no benefit in the work-up of suspected CRS. When radiographic imaging is desired, the consensus documents are consistent in their recommendation of CT as a preferred technique.

Allergy and Immunology Evaluation. The JTFPP document recommends that patients with recurrent RS or CRS be evaluated for underlying allergy.[6] Allergy testing is cited as an optional work-up in the CPG:AS guidelines in cases of CRS or recurrent ARS, with skin testing being the preferred method.[7] The EP³OS guidelines recommend questioning patients with regard to allergies and doing further testing in patients with a history of allergy.[4] The RI provides in-depth review of the association between allergic disease and RS but makes no formal recommendation regarding when such testing should be implemented.[5]

As many as 60% of patients with CRS have substantial allergic sensitivities, primarily to perennial allergens, such as house dust mites, cockroaches, pet dander, and fungi.[79] Presumably, management of concomitant AR might be expected to decrease the frequency of RS through a reduction in nasal mucosal swelling and inflammation adjacent to the sinus outflow tract. Unfortunately, despite the epidemiological data, evidence-based data to support this assumption are somewhat sparse, leading the CPG:AS guidelines to conclude that allergy testing could not be "strongly recommended" but should be considered optional.[7] The BSACI guidelines recommend skin prick testing in all cases of RS; however, it is noted that results should be interpreted in light of clinical history.[8] In our experience, it is not uncommon for patients with CRS to be referred for an allergy evaluation only after having undergone a surgical procedure without benefit. Because many of these patients have perennial allergies, they could have had a better response to medical management of CRS had their allergies been identified in advance of sinus surgery.

A suggested approach would be to evaluate any patient with CRS whose symptoms are not easily controlled by saline irrigations and intranasal medications for underlying allergies. This approach is especially recommended for patients who are being considered for sinus surgery.

The EP^{3}OS, JTFPP, and CPG:AS guidelines recommend immunologic testing in patients with CRS or recurrent ARS in whom aggressive management has failed or who demonstrate recurrent or persistent purulent infections.[4,6,7] An analysis of 79 radiographically confirmed cases of recurrent or refractory RS uncovered a diagnosis of common variable immunodeficiency in 10% of patients and selective IgA deficiency in 6%. Low titers of IgG, IgA, and IgM were noted in 18%, 17%, and 5% of cases, respectively.[80] Sinus symptoms are also highly prevalent among patients infected with the human immunodeficiency virus.[81,82] Laboratory work-up might include quantitative immunoglobulin assays (IgG, IgA, IgM), specific antibody responses to tetanus toxoid and pneumococcal vaccines (both before and after immunization), and assessments of T-cell number and function.[6,7]

Special Testing for AFRS. Only the RI and BSACI guidelines outline diagnostic criteria specific to AFRS. For the RI, these include the presence of at least 1 CRS symptom, the presence of endoscopy-documented allergic mucin and inflammation, skin or blood tests positive for fungus-specific IgE, and no histologic evidence of invasive fungal disease.[5] For the BSACI, these include the presence of CRS with NP; specific antifungal IgE; CT heterogeneity, expansion, or erosion; eosinophilic mucin without fungal invasion; and fungi in sinus contents.[8]

MANAGEMENT OF CRS

The lack of an overall consensus or a succinct algorithm for the treatment of CRS is due in large part to the paucity of controlled studies for this indication. The design and interpretation of CRS clinical trials have been hindered by the inherent heterogeneity of the disease, a lack of uniform definitions for the various subtypes, an incomplete understanding of the underlying pathologies, and a lack of useful and standardized clinical and laboratory end points to measure response to therapy.[83] In 2006, for the first time, the FDA included CRS (without specifying subtypes) in its guidelines for RS studies[84] and began to recognize the validity of some CRS studies. Regardless, it may take time to acquire a sufficient body of reliable clinical data for this indication. Although an FDA-approved treatment for NP (mometasone furoate nasal spray) is currently available, no treatments have been approved by the FDA for CRS.

The EP^{3}OS guidelines put forth treatment recommendations for CRS, categorized into 3 major subtypes (a scheme also adopted in large part by the BSACI guidelines[8]): CRS without NP, CRS with NP, and AFRS. Recommendations are stratified according to disease severity, using a VAS scale of 0 (none) to 10 (most severe). Table 5 summarizes these recommendations along with the less detailed guidance provided by the JTFPP and CPG:AS; levels of evidence and strength of recommendation given by the various guidelines are indicated. Other therapeutic modalities were also graded by the EP^{3}OS guidelines (including antifungal agents, bacterial lysates, mucolytics, and short-term antibiotics), but these were not judged by the EP^{3}OS authors to have clinical relevance and thus are not presented in Table 5.

TREATMENT RECOMMENDATIONS BY EP^{3}OS FOR CRS

CRS Without NP. Management of CRS without NP is divided into 2 categories. For mild symptoms (VAS score, 0-3), recommended initial management consists of intranasal corticosteroids along with nasal saline lavage. If the condition does not improve after 3 months, culture should be performed and long-term macrolide therapy instituted; CT may be useful at this stage. Lack of response to this strategy after another 3 months should prompt further CT evaluation and consideration of sinus surgery. In cases that do respond, ongoing follow-up is recommended, along with continued intranasal corticosteroid use and nasal saline lavage, with or without long-term macrolide therapy.[4] For moderate or severe symptoms (VAS score, >3-10), initial management should include intranasal corticosteroids, nasal saline lavage, culture, and long-term macrolide therapy. If no response is seen after 3 months, further CT evaluation and surgical work-up are warranted. The EP^{3}OS guidelines do not discuss how the results from sinus cultures might affect treatment.

The level of evidence assigned to some therapies by the EP^{3}0S guidelines is open to debate. For instance, the recommendation for long-term macrolide therapy is based on a study by Ragab et al,[101] which was graded as level Ib evidence (based on at least 1 randomized controlled trial). In this trial, patients randomly assigned to medical treatment with erythromycin, alkaline nasal irrigation, and intranasal corticosteroids were found to have symptom scores and endoscopic findings at 6 and 12 months that were not significantly different from scores seen in patients who underwent surgery.[101] However, no sham surgery was performed on the medically treated patients, making it impossible to rule out a placebo effect. Patients who underwent surgery also received medical therapy with erythromycin, intranasal corticosteroids, and alkaline nasal irrigation, and medical therapy late in the study could be tailored to each patient's symptoms, making it difficult to identify a true control group and thus to assess the value of any 1 therapy. These features are atypical for most randomized clinical trials.

TABLE 5. **Summary of Recent Evidence-Based Recommendations for the Treatment of CRS[a,b,c]**

Guidelines[d]		
EP³OS,[4] 2007[e]	CRSsNP Mild (VAS, 0-3) Topical corticosteroids (A/Ib)[85-89] Nasal lavage (A/Ib)[67,90-94] If failure after 3 mo, treat as moderate/severe Moderate/severe (VAS, >3-10) Topical corticosteroids (A/Ib)[85-89] Nasal lavage (A/Ib)[67,90-94] Long-term macrolide therapy (A/Ib)[95-102] Culture Cases that improve Follow-up + nasal lavage, topical corticosteroids ± long-term macrolide therapy	CRScNP Mild (VAS, 0-3) Topical corticosteroid spray for 3 mo (Ib/A)[103-117] If beneficial, continue and review every 6 mo If no improvement, add short course of oral corticosteroids (Ib/A)[118-123] If still no improvement, consider CT; assess as surgical candidate If improved after 1 mo, switch to topical corticosteroid drops (Ib/A);[103-117] review after 3 mo Moderate (VAS, >3-7) Topical corticosteroid drops for 3 mo (Ib/A)[103-117] If beneficial, continue and review every 6 mo If no improvement after 3 mo, add short course of oral corticosteroids (Ib/A)[118-123]; consider CT; and evaluate as surgical candidate (II, not graded)[124] If improved at 1 mo, switch to topical corticosteroid drops (Ib/A)[103-117] Severe (VAS, >7-10) Short course of oral corticosteroids[118-123] + topical corticosteroid for 1 mo[103-117] (Ib/A) If beneficial, topical corticosteroid drops only; review after 3 mo (Ib/A)[103-117] If no improvement, perform CT and evaluate as surgical candidate (II, not graded)[124]
JTFPP,[6] 2005	Antibiotics: role is controversial; may be useful for acute exacerbation of chronic disease (IV,[125] IV[126]) Intranasal corticosteroids: may be modestly beneficial as adjunctive therapy (C) (Ib,[119] IIb[127]) Antihistamines: possible role in CRS if underlying risk factor is allergic rhinitis (D) Topical and oral decongestants: prospective studies evaluating use are lacking (D) Antifungal agents: role has not yet been established	
CPG:AS,[7] 2007	Take preventive measures to minimize symptoms and exacerbations of CRS: saline nasal irrigation (recommendation, B)[6,60,92-94,128-130]; concomitant treatment of any underlying conditions (eg, GERD) (recommendation, B)[131,132]; good hand hygiene to prevent acute viral RS (recommendation, B)[133] Assess the patient for factors that could modify management (eg, allergic rhinitis, cystic fibrosis, immunocompromised state, ciliary dyskinesia, anatomic variation) (recommendation, C)[60,134-164]	

[a] AFRS = allergic fungal RS; CPG:AS = Clinical Practice Guideline: Adult Sinusitis; CRS = chronic RS; CRScNP = CRS with NP; CRSsNP = CRS without NP; CT = computed tomography; EP³OS = European Position Paper on Rhinosinusitis and Nasal Polyps 2007; GERD = gastroesophageal reflux disease; JTFPP = Joint Task Force on Practice Parameters; NP = nasal polyposis; RI = Rhinosinusitis Initiative; RS = rhinosinusitis; VAS = visual analog scale.
[b] No treatment recommendations are provided in the RI 2004 document.
[c] See Table 3 for an explanation of grades of recommendations and levels of evidence.
[d] Only the EP³OS recommendations distinguish between CRSsNP and CRScNP.
[e] Grades of recommendation and levels of evidence in the EP³OS guidelines were provided for the use of therapies for CRScNP and CRSsNP, not the order or duration of these therapies. Order and duration of therapy choices presented here are taken from the treatment algorithm found in the EP³OS guidelines. Evidence levels for these recommendations may be disputed; please refer to the text for details.

The study by Wallwork et al,[102] also cited as Ib evidence, was a randomized, placebo-controlled investigation of 150 mg of roxithromycin vs placebo. In this study, patients in the roxithromycin group showed a statistically significant change from baseline in the Sino-Nasal Outcome Test 20 (SNOT20) score at 12 weeks not seen in the placebo group. In a similar "change from baseline" analysis, the roxithromycin group also showed an improvement in saccharine transit time and nasal endoscopy not seen in the placebo group. However, the statistical analysis in this study was unconventional in that it evaluated the results of each study arm at study end against respective values at baseline rather than a more conventional comparison of the change from baseline in each arm using an analysis of covariance model. Given this limitation, the efficacy of roxithromycin cannot be confirmed by the results of this study.

Studies cited by the EP³OS guidelines as evidence of the efficacy of nasal lavage for CRS with NP also merit a closer look. Bachmann et al[90] randomly assigned 40 patients to nasal irrigation with isotonic Ems salt solution or isotonic sodium chloride solution. Significant improvements from baseline in subjective and objective measurement were seen, but no significant difference was found between groups. No true control group was studied; as the authors noted, it is not possible to find a true placebo because any watery solution would remove secretions and crusts in the nose and produce therapeutic effect. Despite these drawbacks, this study is cited in the EP³OS guidelines as level

Ib evidence. Similarly, the studies by Shoseyov et al[92] and Friedman et al[94] are cited as level Ib evidence. Although both are randomized, double-blind studies, they compare 2 different solutions for nasal irrigation, with no true control. Additionally, the trial by Pinto et al,[93] cited as level Ib, was randomized and controlled but examined normal or buffered hypertonic saline sprays (not irrigation) vs no treatment and found no beneficial effect for either active treatment. However, the randomized controlled studies by Rabago et al[67] (N=62) and Taccariello et al[91] (N=76) cited by the EP³OS guidelines showed significant benefit for nasal lavage vs control.

The evidence base supporting the order and duration of therapies recommended by EP³OS is also unclear. For example, an initial 3-month course of intranasal corticosteroids is recommended for mild symptoms of CRS. The recommendation of intranasal corticosteroids for CRS is cited as level Ib evidence, but the studies cited ranged in duration from 11 days to 20 weeks.[85-89] The utility of the therapy may be supported by level Ib evidence, but no evidence is given for the 3-month duration.

The BSACI recommendations[8] differ from the EP³OS guidelines[4] on the following points: the recommendation for surgery only for treatment failures and the grade A recommendation for long-term antibiotics were both based solely on the study by Ragab et al,[101] and addition of antihistamines for allergic patients is given a grade A recommendation. Additionally, surgery is recommended for AFRS.

CRS With NP. The EP³OS guidelines for managing CRS with NP are generally similar to CRS without NP, with the notable exception that antibiotics are not recommended.[4]

For symptoms of mild severity (VAS score, 0-3), treatment with an intranasal corticosteroid is recommended; if improvement is noted after 3 months, treatment should be continued with follow-up every 6 months. If no improvement is seen within 3 months, a short course of oral corticosteroids for 1 month is recommended. If that too is unsuccessful, CT is recommended, and the patient should be evaluated as a potential surgical candidate.

In cases of symptoms of moderate severity (VAS score, >3-7), topical corticosteroid drops are recommended initially for 3 months, with continued use and follow-up every 6 months thereafter if effective. If no improvement is seen after the initial 3 months, a short course of oral corticosteroids may be added for 1 month. If this strategy fails, CT is recommended, and the patient should be evaluated as a potential surgical candidate. If improvement is noted after the 1-month oral corticosteroid course, the patient can be switched back to topical corticosteroid drops.

Severe cases of CRS with NP (VAS score, >7-10) should initially be managed using a short course (1 month) of oral corticosteroids in combination with topical corticosteroids. If improvement occurs on this regimen alone, the patient may be switched to topical corticosteroids alone. Patients who do not initially show improvement should be evaluated via CT and considered for surgical intervention. After polypectomy, maintenance treatment with intranasal corticosteroids is generally recommended.

Again, the evidence on which EP³OS bases its recommendations for order and duration of therapies merits examination. For example, therapy with oral corticosteroids for CRS with polyps is cited as level Ib evidence on the basis of studies by Benitez et al[122] and Hissaria et al.[123] Both are randomized controlled trials that found significant benefit for oral corticosteroids vs placebo, as seen in objective measures of polyp size and subjective assessment of symptoms; however, both involved 14-day courses of corticosteroids, so it is unclear what evidence contributed to the recommendation of a 1-month course. Further, it is unclear what evidence supports the choice of corticosteroid drops vs sprays at any given point; the evidence level is cited as Ib for topical corticosteroids, and the trials provided as evidence include evaluations of both drops and spray formulations.

In addition to largely adopting the EP³OS recommendations, the BSACI guidelines recommend corticosteroid drops specifically for NP, citing 2 randomized controlled trials that the EP³OS guidelines also cited in recommending "topical" corticosteroids.[4,8,111,114] The addition of oral antihistamines for allergic patients with CRS is given a grade A recommendation, and the use of antileukotrienes is given a grade C recommendation but considered clinically relevant.

AFRS. The EP³OS guidelines[4] do not present a detailed treatment algorithm for AFRS. Surgery is indicated as a first-line treatment, along with topical or systemic antifungal drugs.

Other Guidelines for CRS Management

The JTFPP and CPG:AS guidelines propose very general management strategies for CRS, with no categorization of subtypes by CRS with vs without NP or AFRS. The RI document does not provide specific treatment recommendations.

The JTFPP guidelines[6] indicate that the role of antibiotics in CRS is controversial but that antibiotics may be required for acute exacerbations of CRS. Intranasal corticosteroids are suggested as being modestly beneficial in CRS as an adjunct to antibiotic therapy in cases of recurrent ARS or CRS. The JTFPP guidelines state that antihistamines may have a role in the treatment of CRS when AR is also present because AR and CRS cause overlapping symptoms and AR may predispose patients to the devel-

opment of CRS. (See "Allergy and Immunology Evaluation" for supportive evidence of a relationship between AR and CRS.) The guidelines acknowledge that topical and oral decongestants are often used in both ARS and CRS, although there are insufficient studies to determine their value for these indications. The guidelines also conclude that the role of antifungal agents in CRS has not been established.

The CPG:AS guidelines[7] offer no specific treatment recommendations for CRS but rather try to minimize symptoms and prevent exacerbations by focusing on preventive measures, such as saline nasal irrigation, concomitant management of underlying conditions (eg, gastroesophageal reflux disease), and good hand hygiene to prevent AVRS. A recommendation is made to evaluate patients with CRS for the presence of contributory factors or other disease states that might complicate disease management (eg, AR, cystic fibrosis, immunodeficiency, ciliary dyskinesia, or anatomic variations).

CONTINUING RESEARCH

Many issues remain to be addressed in the field of RS management, particularly CRS. An encouraging upsurge in the number of CRS-oriented investigational studies has occurred since publication of the most recent RS guidelines. Promising areas of investigation in CRS include studies of the role of bacterial biofilms, immune hyperresponsiveness to colonizing fungi, and defects in innate immunity in the initiation or persistence of CRS.

Many recent studies have been conducted in patients with CRS.[165] Among the interventions being evaluated are topical antibiotic and antifungal agents, maxillary sinus irrigation or nasal spray, oral corticosteroids, a recombinant DNA–derived humanized IgG1κ monoclonal antibody (omalizumab), a novel leukotriene receptor antagonist (pranlukast), and the use of probiotics.[165] However, lack of a clear consensus on the definition of subgroups within the CRS patient population, demonstrated by the varying definitions proposed by these guidelines, continues to hinder study design and limit the conclusions that can be drawn. The RI document[9] presents recommendations to address these issues, including detailed guidance on study designs specific for subtypes of CRS and specific forms of treatment (eg, antimicrobial vs anti-inflammatory). These recommendations can be used in designing future trials, with the goal of evaluating appropriate interventions for the various etiologies and pathologies that can produce CRS. In addition to the efforts of the RI, the FDA published a 2006 guidance document on clinical trials of nonantibiotic agents for CRS.[84] It is hoped that progress toward clinical trials will follow from this work because pharmaceutical and biotechnical companies have pointed to the lack of consensus on definitions and study designs for CRS as a major stumbling block to drug development. Although progress has been slow, expert panels have shown great motivation to advance this field, and there has been an uptick in funding from the National Institutes of Health for basic CRS investigations.[165]

CONCLUSION

Current consensus and evidence-based guidelines are in agreement with regard to the diagnosis and treatment of ARS. The efficacy of intranasal corticosteroids has been well established by clinical trial data, and all 4 guidelines with evidence-based treatment recommendations (EP^{3}OS, JTFPP, CPG:AS, and BSACI) advise their use in ARS; these 4 guidelines also recommend antibiotics for patients presenting with severe ARS symptoms. An issue of great concern in ARS, in which most cases by far are viral and self-limiting, remains the continued high rate at which clinicians overprescribe antibiotics, a point on which the guidelines agree. However, although all the guidelines recognize symptom severity as a factor for determining when to use antibiotics, the means recommended for determining severity vary, from VAS in the EP^{3}OS, BSACI, and RI guidelines to various possible scales in the CPG:AS guidelines to specific symptoms (eg, fever, purulent nasal discharge, facial pain or tenderness, and periorbital swelling) in the JTFPP guidelines. Thus, clinicians are presented with discordant guidance and must rely on clinical experience and judgment.

In contrast, consensus and evidence-based guidelines regarding CRS are much less congruent, possibly because of the greater complexity and heterogeneity of this condition and the paucity of clinical trials in this area. No overall consensus has been reached regarding treatment of CRS. The recommendations made by the EP^{3}OS guidelines (and subsequently by the BSACI guidelines) for pharmacological treatment of CRS help fill a void in the literature but are sometimes lacking in rigorous evidence (eg, in their consideration of long-term use of macrolides). Few clinical trials have been conducted comparing the treatment of CRS without NP, CRS with NP, and AFRS as separate entities, although there has been a strong push to promote such trials.[9] The guidelines also vary in their consideration of surgery, and one (CPG:AS) makes no recommendation whatsoever regarding surgery. Many questions remain regarding optimal patient selection and surgical strategies. Nevertheless, the publication of 5 consensus documents within the past 6 years is a very good sign, and substantial progress has been made toward consensus disease definitions and basic investigations in CRS. The detailed CRS subgroup

classification scheme and diagnostic methods proposed by the RI may be particularly useful in this regard. The lack of category I evidence for therapeutic modalities for CRS and the lack of understanding of CRS pathophysiology are continuing issues. Future clinical research should establish appropriate diagnostic testing strategies to identify pathogenic factors (eg, allergic, infectious, fungal) and ascertain which treatments are most effective for each. As a practical matter, we consider allergy testing (as recommended by the JTFPP, EP^{3}OS, and BSACI guidelines) to be valuable for patients with long-standing or recurrent symptoms, especially when these symptoms are uncontrolled by topical saline and intranasal corticosteroids. Such testing is likely to play a part in forthcoming treatment strategies that are more closely directed to the underlying cause of CRS. It is hoped that the next generation of consensus guidelines will have a much greater knowledge base on which to draw to refine recommendations for practicing clinicians, with the ultimate goal of improving patient health outcomes.

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REFERENCES

1. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. National Center for Health Statistics. *Vital Health Stat 10.* 2009;(242):1-157. www.cdc.gov/nchs/data/series/sr_10/sr10_242.pdf. Accessed February 16, 2011.
2. Bhattacharyya N. Contemporary assessment of the disease burden of sinusitis. *Am J Rhinol Allergy.* 2009;23(4):392-395.
3. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg.* 1995;113(1):104-109.
4. Fokkens W, Lund V, Mullol J; European Position Paper on Rhinosinusitis and Nasal Polyps Group. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinology.* 2007;45(suppl 20):1-139. http://www.ep3os.org/EPOS2007.pdf. Accessed February 16, 2011.
5. Meltzer EO, Hamilos DL, Hadley JA, et al; American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Otolaryngic Allergy (AAOA), the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS), the American College of Allergy, Asthma and Immunology (ACAAI), and the American Rhinologic Society (ARS). Rhinosinusitis: establishing definitions for clinical research and patient care. *J Allergy Clin Immunol.* 2004;114(6, suppl):S155-S212.
6. Slavin RG, Spector SL, Bernstein IL, et al; American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol.* 2005;116(6, suppl):S13-S47.
7. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg.* 2007;137(3, suppl):S1-S31.
8. Scadding GK, Durham SR, Mirakian R, et al; British Society for Allergy and Clinical Immunology. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clin Exp Allergy.* 2008;38(2):260-275.
9. Meltzer EO, Hamilos DL, Hadley JA, et al; Rhinosinusitis Initiative. Rhinosinusitis: developing guidance for clinical trials. *J Allergy Clin Immunol.* 2006;118(5, suppl):S17-S61.
10. Lim M, Lew-Gor S, Darby Y, Brookes N, Scadding G, Lund VJ. The relationship between subjective assessment instruments in chronic rhinosinusitis. *Rhinology.* 2007;45(2):144-147.
11. Gwaltney JM Jr, Hendley JO, Simon G, Jordan WS Jr. Rhinovirus infections in an industrial population; II: Characteristics of illness and antibody response. *JAMA.* 1967;202(6):494-500.
12. Berger G, Berger RL. The contribution of flexible endoscopy for diagnosis of acute bacterial rhinosinusitis. *Eur Arch Otorhinolaryngol.* 2011;268(2):235-240.
13. Benninger MS, Appelbaum PC, Denneny JC, Osguthorpe DJ, Stankiewicz JA. Maxillary sinus puncture and culture in the diagnosis of acute rhinosinusitis: the case for pursuing alternative culture methods. *Otolaryngol Head Neck Surg.* 2002;127(1):7-12.
14. Katholm M, Brofeldt S. Canine fossa puncture: an alternative to antro-nasal puncture of the maxillary sinus. *Ear Nose Throat J.* 1991;70(5):325-326.
15. Singhal D, Douglas R, Robinson S, Wormald PJ. The incidence of complications using new landmarks and a modified technique of canine fossa puncture. *Am J Rhinol.* 2007;21(3):316-319.
16. Gill JM, Fleischut P, Haas S, Pellini B, Crawford A, Nash DB. Use of antibiotics for adult upper respiratory infections in outpatient settings: a national ambulatory network study. *Fam Med.* 2006;38(5):349-354.
17. Ashworth M, Charlton J, Ballard K, Latinovic R, Gulliford M. Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK general practices 1995-2000. *Br J Gen Pract.* 2005;55(517):603-608.
18. Inanli S, Ozturk O, Korkmaz M, et al. The effects of topical agents of fluticasone propionate, oxymetazoline, and 3% and 0.9% sodium chloride solutions on mucociliary clearance in the therapy of acute bacterial rhinosinusitis in vivo. *Laryngoscope.* 2002;112(2):320-325.
19. Wiklund L, Stierna P, Berglund R, Westrin KM, Tonnesson M. The efficacy of oxymetazoline administered with a nasal bellows container and combined with oral phenoxymethyl-penicillin in the treatment of acute maxillary sinusitis. *Acta Otolaryngol Suppl.* 1994;515:57-64.
20. McCormick DP, John SD, Swischuk LE, Uchida T. A double-blind, placebo-controlled trial of decongestant-antihistamine for the treatment of sinusitis in children. *Clin Pediatr (Phila).* 1996;35(9):457-460.
21. Pneumatikos I, Konstantonis D, Dragoumanis C, Danielides V, Bouros D. Preventing nosocomial sinusitis in the ICU [letter reply]. *Intensive Care Med.* 2006;32(9):1452-1453.
22. Adam P, Stiffman M, Blake RL Jr. A clinical trial of hypertonic saline nasal spray in subjects with the common cold or rhinosinusitis. *Arch Fam Med.* 1998;7(1):39-43.
23. Axelsson A, Grebelius N, Jensen C, Melin O, Singer F. Treatment of acute maxillary sinusitis. IV. Ampicillin, cephradine and erythromycinestolate with and without irrigation. *Acta Otolaryngol.* 1975;79(5-6):466-472.
24. Qvarnberg Y, Kantola O, Salo J, Toivanen M, Valtonen H, Vuori E. Influence of topical steroid treatment on maxillary sinusitis. *Rhinology.* 1992;30(2):103-112.
25. Meltzer EO, Orgel HA, Backhaus JW, et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. *J Allergy Clin Immunol.* 1993;92(6):812-823.
26. Barlan IB, Erkan E, Bakir M, et al. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Ann Allergy Asthma Immunol.* 1997;78(6):598-601.
27. Meltzer EO, Charous BL, Busse WW, et al; The Nasonex Sinusitis Group. Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. *J Allergy Clin Immunol.* 2000;106(4):630-637.
28. Dolor RJ, Witsell DL, Hellkamp AS, et al; Ceftin and Flonase for Sinusitis (CAFFS) Investigators. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis: the CAFFS Trial: a randomized controlled trial. *JAMA.* 2001;286(24):3097-3105.
29. Nayak AS, Settipane GA, Pedinoff A, et al. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. *Ann Allergy Asthma Immunol.* 2002;89(3):271-278.
30. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin and placebo. *J Allergy Clin Immunol.* 2005;116(6):1289-1295.
31. Williams JW Jr, Aguilar C, Cornell J, et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev.* 2003;(2):CD000243.
32. Lindbaek M, Hjortdahl P, Johnsen UL. Randomised, double blind, placebo controlled trial of penicillin V and amoxicillin in treatment of acute sinus infections in adults. *BMJ.* 1996;313(7053):325-329.
33. van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, et al. Primary care-based randomized placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. *Lancet.* 1997;349(9053):683-687.
34. Axelsson A, Chidekel N, Grebelius N, Jensen C. Treatment of acute maxillary sinusitis: a comparison of four different methods. *Acta Otolaryngol.* 1970;70(1):71-76.

35. Gehanno P, Beauvillain C, Bobin S, et al. Short therapy with amoxicillin-clavulanate and corticosteroids in acute sinusitis: results of a multicentre study in adults. *Scand J Infect Dis.* 2000;32(6):679-684.

36. Klossek JM, Desmonts-Gohler C, Deslandes B, et al. Treatment of functional signs of acute maxillary rhinosinusitis in adults: efficacy and tolerance of administration of oral prednisone for 3 days [article in French]. *Presse Med.* 2004;33(5):303-309.

37. Braun JJ, Alabert JP, Michel FB, et al. Adjunct effect of loratadine in the treatment of acute sinusitis in patients with allergic rhinitis. *Allergy.* 1997;52(6):650-655.

38. Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg.* 2000;123(suppl):S1-S32.

39. American Academy of Pediatrics; Subcommittee on the Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. *Pediatrics.* 2001;108(3):798-808.

40. Hickner JM, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for acute rhinosinusitis in adults: background. *Ann Intern Med.* 2001;134(6):498-505.

41. Benninger MS, Sedory-Holzer SE, Lau J. Diagnosis and treatment of uncomplicated acute bacterial rhinosinusitis: summary of the Agency for Health Care Policy and Research evidence-based report. *Otolaryngol Head Neck Surg.* 2000;122(1):1-7.

42. Spector SL, Bernstein IL, Li JT, et al; Joint Task Force on Practice Parameters. Parameters for the diagnosis and management of sinusitis. *J Allergy Clin Immunol.* 1998;102(6, pt 2):S107-S144.

43. Wald ER, Mason EO Jr, Bradley JS, Barson WJ, Kaplan SL; US Pediatric Multicenter Pneumococcal Surveillance Group. Acute otitis media caused by *Streptococcus pneumoniae* in children's hospitals between 1994 and 1997. *Pediatr Infect Dis J.* 2001;20(1):34-39.

44. Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Applebaum PC. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 US surveillance study. *Antimicrob Agents Chemother.* 1999;43(8):1901-1908.

45. de Ferranti SD, Ioannidis JPA, Lau J, et al. Are amoxicillin and folate inhibitors as effective as other antibiotics for acute sinusitis? a meta-analysis. *BMJ.* 1998;317(7159):632-637.

46. Hoban DJ, Doern GV, Fluit AC, Roussel-Delallex M, Jones RN. Worldwide prevalence of antimicrobial resistance in *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* in the SENTRY Antimicrobial Surveillance Program, 1997-1999. *Clin Infect Dis.* 2001;32(suppl 2):S81-S93.

47. Camacho AE, Cobo R, Otte J, et al. Clinical comparison of cefuroxime axetil and amoxicillin/clavulanate in the treatment of patients with acute bacterial maxillary sinusitis. *Am J Med.* 1992;93(3):271-276.

48. Gwaltney JM Jr, Savolainen S, Rivas P, et al. Comparative effectiveness and safety of cefdinir and amoxicillin-clavulanate in treatment of acute community-acquired bacterial sinusitis. *Antimicrob Agents Chemother.* 1997; 41(7):1517-1520.

49. Clark JP, Langston E. Ketolides: a new class of antibacterial agents for treatment of community-acquired respiratory tract infections in a primary case setting. *Mayo Clin Proc.* 2003;78(9):1113-1124.

50. Bascom R, Wachs M, Naclerio RM, et al. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol.* 1988;81:580-589.

51. Pipkorn U, Proud D, Lichtenstein LL, et al. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *N Engl J Med.* 1987;316:1506-1510.

52. Baroody FM, Cruz AA, Lichtenstein LL, et al. Intranasal beclomethasone inhibits antigen-induced nasal hyperresponsiveness to histamine. *J Allergy Clin Immunol.* 1992;90:373-376.

53. Siegel SC. Topical intranasal corticosteroid therapy in rhinitis. *J Allergy Clin Immunol.* 1988;81:984-991.

54. Juniper EF, Guyatt GH, O'Byrne PM, Viveiros M. Aqueous beclomethasone dipropionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1990;86:380-386.

55. Diaz I, Bamberger DM. Acute sinusitis. *Semin Respir Infect.* 1995;10(1): 14-20.

56. Malm L. Pharmacological background to decongesting and anti-inflammatory treatment of rhinitis and sinusitis. *Acta Otolaryngol Suppl.* 1994;515: 53-55.

57. Joint Commission Web site. www.JCAHO.org/. Accessed February 16, 2011.

58. Loesser JD, ed. *Bonica's Management of Pain.* 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001.

59. Snow V, Mottur-Pilson C, Hickner JM. Principles of appropriate antibiotic use for acute sinusitis in adults. *Ann Intern Med.* 2001;134:495-497.

60. Fokkens W, Lund V, Bachert C, et al. EAACI position paper on rhinosinusitis and nasal polyps: executive summary. *Allergy.* 2005;60(5):583-601.

61. Hickner JM, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for acute rhinosinusitis in adults: background. *Ann Intern Med.* 2001;134:498-505.

62. Ip S, Fu L, Balk E, Chew P, DeVine D, Lau J. *Update on Acute Bacterial Rhinosinusitis.* Evidence Report/Technology Assessment No. 124. AHRQ Publication No. 05-E020-2. Rockville, MD: Agency for Healthcare Research and Quality; June 2005. www.ahrq.gov/clinic/epcsums/rhinoupsum.htm. Accessed March 17, 2011.

63. de Sutter AI, de Meyere MJ, Christiaens TC, et al. Does amoxicillin improve outcomes in patients with purulent rhinorrhea? a pragmatic, randomized double-blind controlled trial in family practice. *J Fam Pract.* 2002;51(4): 317-323.

64. Lindbaek M, Kaastad E, Dolvik S, et al. Antibiotic treatment of patients with mucosal thickening in the paranasal sinuses, and validation of cut-off points in sinus CT. *Rhinology.* 1998;36(1):7-11.

65. Merenstein D, Whittaker C, Chadwell T, et al. Are antibiotics beneficial for patients with sinusitis complaints? a randomized double-blind clinical trial. *J Fam Pract.* 2005;54(2):144-151.

66. Varonen H, Kunnamo I, Savolainen S, et al. Treatment of acute rhinosinusitis diagnosed by clinical criteria or ultrasound in primary care. *Scand J Prim Health Care.* 2003;21(2):121-126.

67. Rabago D, Zgierska A, Mundt M, et al. Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: a randomized controlled trial. *J Fam Pract.* 2002;51(12):1049-1055.

68. Keojampa BK, Nguyen MH, Ryan MW. Effects of buffered saline solution on nasal mucociliary clearance and nasal airway patency. *Otolaryngol Head Neck Surg.* 2004;131(5):679-682.

69. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered hypertonic saline solution. *Laryngoscope.* 1997;107(4):500-503.

70. Wabnitz DA, Wormald PJ. A blinded, randomized, controlled study of the effect of buffered 0.9% and 3% sodium chloride intranasal sprays on ciliary beat frequency. *Laryngoscope.* 2005;115(5):803-805.

71. Eccles R, Jawad MS, Jawad SS, et al. Efficacy and safety of single and multiple doses of pseudoephedrine in the treatment of nasal congestion associated with common cold. *Am J Rhinol.* 2005;19(1):25-31.

72. Jawad SS, Eccles R. Effect of pseudoephedrine on nasal airflow in patients with nasal congestion associated with common cold. *Rhinology.* 1998;36(2): 73-76.

73. Latte J, Taverner D, Slobodian P, et al. A randomized, double-blind, placebo-controlled trial of pseudoephedrine in coryza. *Clin Exp Pharmacol Physiol.* 2004;31(7):429-432.

74. Sperber SJ, Turner RB, Sorrentino JV, et al. Effectiveness of pseudoephedrine plus acetaminophen for treatment of symptoms attributed to the paranasal sinuses associated with the common cold. *Arch Fam Med.* 2000;9(10):979-985.

75. Taverner D, Danz C, Economos D. The effects of oral pseudoephedrine on nasal patency in the common cold: a double-blind single-dose placebo-controlled trial. *Clin Otolaryngol Allied Sci.* 1999;24(1):47-51.

76. Zeiger RS. Prospects for ancillary treatment of sinusitis in the 1990's. *J Allergy Clin Immunol.* 1992;90(3, pt 2):478-495.

77. Shin SH, Ponikau JU, Sherris DA, et al. Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. *J Allergy Clin Immunol.* 2004;114(6):1369-1375.

78. Bhattacharyya N, Lee LN. Evaluating the diagnosis of chronic rhinosinusitis based on clinical guidelines and endoscopy. *Otolaryngol Head Neck Surg.* 2010;143(1):147-151.

79. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. *Otolaryngol Head Neck Surg.* 2000; 123(6):687-691.

80. Chee L, Graham SM, Carothers DG, Ballas ZK. Immune dysfunction in refractory sinusitis in a tertiary care setting. *Laryngoscope.* 2001; 111(2):233-235.

81. Del Borgo C, Del Forno A, Ottaviani F, Fantoni M. Sinusitis in HIV-infected patients. *J Chemother.* 1997;9(2):83-88.

82. Zurlo JJ, Feuerstein IM, Lebovics R, Lane HC. Sinusitis in HIV-1 infection. *Am J Med.* 1992;93(2):157-162.

83. Rank MA, Adolphson CR, Kita H. Antifungal therapy for chronic rhinosinusitis: the controversy persists. *Curr Opin Allergy Clin Immunol.* 2009; 9(1):67-72.

84. US Department of Health and Human Services (DHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). FDA Web site. Guidance for industry: Sinusitis: designing clinical development programs of nonantimicrobial drugs for treatment; published November 2006. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation /Guidances/ucm072037.pdf. Accessed February 16, 2011.

85. Cuenant G, Stipon JP, Plante-Longchamp G, Baudoin C, Guerrier Y. Efficacy of endonasal neomycin-tixocortol pivalate irrigation in the treatment of chronic allergic and bacterial sinusitis. *ORL J Otorhinolaryngol Relat Spec.* 1986;48(4):226-232.

86. Sykes DA, Wilson R, Chan KL, Mackay IS, Cole PJ. Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis: a controlled study. *Lancet.* 1986;2(8503):359-360.

87. Parikh A, Scadding GK, Darby Y, Baker RC. Topical corticosteroids in chronic rhinosinusitis: a randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray. *Rhinology.* 2001;39(2):75-79.

88. Lavigne F, Cameron L, Renzi PM, et al. Intrasinus administration of topical budesonide to allergic patients with chronic rhinosinusitis following surgery. *Laryngoscope.* 2002;112(5):858-864.

89. Lund VJ, Black JH, Szabo LZ, Schrewelius C, Akerlund A. Efficacy and tolerability of budesonide aqueous nasal spray in chronic rhinosinusitis patients. *Rhinology.* 2004;42(2):57-62.

90. Bachmann G, Hommel G, Michel O. Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. *Eur Arch Otorhinolaryngol.* 2000;257(10):537-541.

91. Taccariello M, Parikh A, Darby Y, Scadding G. Nasal douching as a valuable adjunct in the management of chronic rhinosinusitis. *Rhinology.* 1999;37(1):29-32.

92. Shoseyov D, Bibi H, Shai P, Shoseyov N, Shazberg G, Hurvitz H. Treatment with hypertonic saline versus normal saline nasal wash of pediatric chronic sinusitis. *J Allergy Clin Immunol.* 1998;101(5):602-605.

93. Pinto JM, Elwany S, Baroody FM, Naclerio RM. Effects of saline sprays on symptoms after endoscopic sinus surgery. *Am J Rhinol.* 2006; 20(2):191-196.

94. Friedman M, Vidyasagar R, Joseph N. A randomized, prospective, double-blind study on the efficacy of Dead Sea salt nasal irrigations. *Laryngoscope.* 2006;116(6):878-882.

95. Gandhi A, Brodsky L, Ballow M. Benefits of antibiotic prophylaxis in children with chronic sinusitis: assessment of outcome predictors. *Allergy Proc.* 1993;14(1):37-43.

96. Nishi K, Mizuguchi M, Tachibana H, et al. Effect of clarithromycin on symptoms and mucociliary transport in patients with sino-bronchial syndrome [in Japanese]. *Nihon Kyobu Shikkan Gakkai Zasshi.* 1995;33(12):1392-1400.

97. Scadding GK, Lund VJ, Darby YC. The effect of long-term antibiotic therapy upon ciliary beat frequency in chronic rhinosinusitis. *J Laryngol Otol.* 1995;109(1):24-26.

98. Ichimura K, Shimazaki Y, Ishibashi T, Higo R. Effect of new macrolide roxithromycin upon nasal polyps associated with chronic sinusitis. *Auris Nasus Larynx.* 1996;23:48-56.

99. Hashiba M, Baba S. Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis. *Acta Otolaryngol Suppl.* 1996;525:73-78.

100. Suzuki H, Shimomura A, Ikeda K, Oshima T, Takasaka T. Effects of long-term low-dose macrolide administration on neutrophil recruitment and IL-8 in the nasal discharge of chronic sinusitis patients. *Tohoku J Exp Med.* 1997;182(2):115-124.

101. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope.* 2004;114(5):923-930.

102. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope.* 2006;116(2):189-193.

103. Mygind N, Pedersen CB, Prytz S, Sorensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. *Clin Allergy.* 1975;5(2):159-164.

104. Deuschl H, Drettner B. Nasal polyps treated by beclomethasone nasal aerosol. *Rhinology.* 1977;15(1):17-23.

105. Holopainen E, Grahne B, Malmberg H, Makinien J, Lindqvist N. Budesonide in the treatment of nasal polyposis. *Eur J Respir Dis Suppl.* 1982; 122:221-228.

106. Vendelo Johansen L, Illum P, Kristensen S, Winther L, Vang Petersen S, Synnerstad B. The effect of budesonide (Rhinocort) in the treatment of small and medium-sized nasal polyps. *Clin Otolaryngol.* 1993;18(6):524-527.

107. Lildholdt T, Rundcrantz H, Lindqvist N. Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. *Clin Otolaryngol.* 1995;20(1):26-30.

108. Holmberg K, Juliusson S, Balder B, Smith DL, Richards DH, Karlsson G. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. *Ann Allergy Asthma Immunol.* 1997;78(3):270-276.

109. Tos M, Svendstrup F, Arndal H, et al. Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. *Am J Rhinol.* 1998;12(3):183-189.

110. Lund VJ, Flood J, Sykes AP, Richards DH. Effect of fluticasone in severe polyposis. *Arch Otolaryngol Head Neck Surg.* 1998;124(5):513-518.

111. Keith P, Nieminen J, Hollingworth K, Dolovich J. Efficacy and tolerability of fluticasone propionate nasal drops 400 microgram once daily compared with placebo for the treatment of bilateral polyposis in adults. *Clin Exp Allergy.* 2000;30(10):1460-1468.

112. Penttila M, Poulsen P, Hollingworth K, Holmstrom M. Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 microg once daily and twice daily in the treatment of bilateral nasal polyposis: a placebo-controlled randomized study in adult patients. *Clin Exp Allergy.* 2000; 30(1):94-102.

113. Hadfield PJ, Rowe-Jones JM, Mackay IS. A prospective treatment trial of nasal polyps in adults with cystic fibrosis. *Rhinology.* 2000;38(2):63-65.

114. Aukema AAC, Mulder PGH, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. *J Allergy Clin Immunol.* 2005;115(5):1017-1023.

115. Small CB, Hernandez J, Reyes A, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J Allergy Clin Immunol.* 2005;116(6):1275-1281.

116. Stjarne P, Mosges R, Jorissen M, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg.* 2006;132(2):179-185.

117. Stjarne P, Blomgren K, Caye-Thomasen P, Salo S, Soderstrom T. The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. *Acta Otolaryngol.* 2006;126(6):606-612.

118. Lildholdt T, Fogstrup J, Gammelgaard N, Kortholm B, Ulsoe C. Surgical versus medical treatment of nasal polyps. *Acta Otolaryngol.* 1988; 105(1-2):140-143.

119. Lildholdt T, Rundcrantz H, Bende M, Larsen K. Glucocorticoid treatment for nasal polyps; the use of topical budesonide powder, intramuscular betamethasone and surgical treatment. *Arch Otolaryngol Head Neck Surg.* 1997;123(6):595-603.

120. van Camp C, Clement PA. Results of oral steroid treatment in nasal polyposis. *Rhinology.* 1994;32(1):5-9.

121. Damm M, Jungehulsing M, Eckel HE, Schmidt M, Theissen P. Effects of systemic steroid treatment in chronic polypoid rhinosinusitis evaluated with magnetic resonance imaging. *Otolaryngol Head Neck Surg.* 1999; 120(4):517-523.

122. Benitez P, Alobid I, De Haro J, et al. A short course of oral prednisone followed by intranasal budesonide is an effective treatment of severe nasal polyps. *Laryngoscope.* 2006;116(5):770-775.

123. Hissaria P, Smith W, Wormald PJ, et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. *J Allergy Clin Immunol.* 2006;118(1):128-133.

124. Hopkins C, Browne JP, Slack R, et al. Complications of surgery for nasal polyposis and chronic rhinosinusitis: the results of a national audit in England and Wales. *Laryngoscope.* 2006;116(8):1494-1499.

125. Wald ER. Chronic sinusitis in children. *J Pediatr.* 1995;127(3):339-347.

126. Gwaltney JM Jr. Acute community-acquired sinusitis. *Clin Infect Dis.* 1996;23(6):1209-1225.

127. Ruhno J, Anderson B, Denburg J, et al. A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. *J Allergy Clin Immunol.* 1990;86(6, pt 1):946-953.

128. Benninger MS, Anon J, Mabry RL. The medical management of rhinosinusitis. *Otolaryngol Head Neck Surg.* 1997;117(suppl):S41-S49.

129. Papsin B, McTavish A. Saline nasal irrigation. *Can Fam Physician.* 2003;49:168-173.

130. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. *Laryngoscope*. 2000;110(7):1189-1193.

131. Weaver EM. Association between gastroesophageal reflux and sinusitis, otitis media, and laryngeal malignancy: a systematic review of the evidence. *Am J Med*. 2003;115(suppl 3A):81S-89S.

132. DiBaise JK, Olusola BF, Huerter JV, et al. Role of GERD in chronic resistant sinusitis: a prospective, open label, pilot trial. *Am J Gastroenterol*. 2002;97(4):843-850.

133. Pittet D, Allegranzi B, Sax H, et al. Evidence-based model for hand transmission during patient care and the role of improved practices. *Lancet Infect Dis*. 2006;6(10):641-652.

134. Krouse JH. Computed tomography stage, allergy testing, and quality of life in patients with sinusitis. *Otolaryngol Head Neck Surg*. 2000; 123(4):389-392.

135. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. *Otolaryngol Head Neck Surg*. 2000; 123(6):687-691.

136. Subramanian HN, Schechtman KB, Hamilos DL. A retrospective analysis of treatment outcomes and time to relapse after intensive medical treatment for chronic sinusitis. *Am J Rhinol*. 2002;16(6):303-312.

137. Furukawa CT, Sharpe M. Bierman CW, et al. Allergic patients have more frequent infections than non-allergic patients [abstract]. *J Allergy Clin Immunol*. 1992;89:322.

138. Gutman M, Torres A, Keen KJ, et al. Prevalence of allergy in patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2004;130(5):545-552.

139. Marple BF. Allergy and the contemporary rhinologist. *Otolaryngol Clin North Am*. 2003;36(5):941-955.

140. Calhoun K. Diagnosis and management of sinusitis in the allergic patient. *Otolaryngol Head Neck Surg*. 1992;107(6, pt 2):850-854.

141. Ramadan HH, Fornelli R, Ortiz AO, et al. Correlation of allergy and severity of sinus disease. *Am J Rhinol*. 1999;13(5):345-347.

142. Slavin RG. Resistant rhinosinusitis: what to do when usual measures fail. *Allergy Asthma Proc*. 2003;24(5):303-306.

143. Coste A, Gilain L, Roger G, et al. Endoscopic and CT-scan evaluation of rhinosinusitis in cystic fibrosis. *Rhinology*. 1995;33(3):152-156.

144. Armenaka M, Grizzanti J, Rosenstreich DL. Serum immunoglobulins and IgG subclass levels in adults with chronic sinusitis: evidence for decreased IgG3 levels. *Ann Allergy*. 1994;72(6):507-514.

145. Chee L, Graham SM, Carothers DG, et al. Immune dysfunction in refractory sinusitis in a tertiary care setting. *Laryngoscope*. 2001;111(2):233-235.

146. Tahkokallio O, Seppala IJ, Sarvas H, et al. Concentrations of serum immunoglobulins and antibodies to pneumococcal capsular polysaccharides in patients with recurrent or chronic sinusitis. *Ann Otol Rhinol Laryngol*. 2001;110(7, pt 1):675-681.

147. Armengot M, Juan G, Carda C, et al. Young's syndrome: a further cause of chronic rhinosinusitis. *Rhinology*. 1996;34(1):35-37.

148. Braverman I, Wright ED, Wang CG, et al. Human nasal ciliary-beat frequency in normal and chronic sinusitis subjects. *J Otolaryngol*. 1998;27(3):145-152.

149. Mahakit P, Pumhirun P. A preliminary study of nasal mucociliary clearance in smokers, sinusitis and allergic rhinitis patients. *Asian Pac J Allergy Immunol*. 1995;13(2):119-121.

150. Milgrim LM, Rubin JS, Small CB. Mucociliary clearance abnormalities in the HIV-infected patient: a precursor to acute sinusitis. *Laryngoscope*. 1995;105(11):1202-1208.

151. Dastidar P, Heinonen T, Numminen J, et al. Semi-automatic segmentation of computed tomographic images in volumetric estimation of nasal airway. *Eur Arch Otorhinolaryngol*. 1999;256(4):192-198.

152. Calhoun KH, Waggenspack GA, Simpson CB, et al. CT evaluation of the paranasal sinuses in symptomatic and asymptomatic populations. *Otolaryngol Head Neck Surg*. 1991;104(4):480-483.

153. Bingham B, Shankar L, Hawke M. Pitfalls in computed tomography of the paranasal sinuses. *J Otolaryngol*. 1991;20(6):414-418.

154. Kaliner M. Treatment of sinusitis in the next millennium. *Allergy Asthma Proc*. 1998;19(4):181-184.

155. Druce HM. Diagnosis of sinusitis in adults: history, physical examination, nasal cytology, echo, and rhinoscope. *J Allergy Clin Immunol*. 1992;90(3, pt 2):436-441.

156. Nayak SR, Kirtane MV, Ingle MV. Functional endoscopic sinus surgery: I (anatomy, diagnosis, evaluation and technique). *J Postgrad Med*. 1991;37(1):26-30.

157. Elahi M, Frenkiel S, Remy H, et al. Development of a standardized ProForma for reporting computerized tomographic images of the paranasal sinuses. *J Otolaryngol*. 1996;25(2):113-120.

158. Goldstein JH, Phillips CD. Current indications and techniques in evaluating inflammatory disease and neoplasia of the sinonasal cavities. *Curr Probl Diagn Radiol*. 1998;27(2):41-71.

159. Ide C, Trigaux JP, Eloy P. Chronic sinusitis: the role of imaging. *Acta Otorhinolaryngol Belg*. 1997;51(4):247-258.

160. Melhem ER, Oliverio PJ, Benson ML, et al. Optimal CT evaluation for functional endoscopic sinus surgery. *AJNR Am J Neuroradiol*. 1996; 17(1):181-188.

161. Nussenbaum B, Marple BF, Schwade ND. Characteristics of bony erosion in allergic fungal rhinosinusitis. *Otolaryngol Head Neck Surg*. 2001;124(2):150-154.

162. Zinreich SJ. Imaging for staging of rhinosinusitis. *Ann Otol Rhinol Laryngol Suppl*. 2004;193:19-23.

163. Senior BA, Kennedy DW. Management of sinusitis in the asthmatic patient. *Ann Allergy Asthma Immunol*. 1996;77(1):6-15.

164. Sipila J, Antila J, Suonpaa J. Pre- and postoperative evaluation of patients with nasal obstruction undergoing endoscopic sinus surgery. *Eur Arch Otorhinolaryngol*. 1996;253(4-5):237-239.

165. Chronic rhinosinusitis. ClinicalTrials.gov Web site. http://clinicaltrials.gov/ct2/results?term=chronic+rhinosinusitis. Accessed February 16, 2011.